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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,529	08/04/1999	SUSAN MARY KINGSMAN	9192.9USWO	7151

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 03/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/254,529	Applicant(s) KINGSMAN ET AL.
	Examiner S. Kaushal	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other

DETAILED ACTION

Continued Prosecution Application

The request filed on 12/31/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09254529 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's response filed on 01/01/01 has been acknowledged.

Claims 1-10 and 12-23 were canceled.
Claims 24-41 were newly filed.
Claims 24-41 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The references cited herein are of record in a prior Office action.

*If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED.*

Applicant's arguments filed 12/31/01 have been fully considered but they are not persuasive, for the reasons of record as set forth in the earlier office action (Paper No.12, 07/27/01

Claim Rejections - 35 U.S.C. § 112

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a retroviral particle encoding a nucleotide sequence of interest, does not reasonably provide enablement for a retroviral particle that encodes a therapeutic gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention **commensurate in scope** with these claims for the same reasons of record as set forth in the earlier official action mailed on Paper No.9, 11/15/00.

Claim 28 recites "therapeutic gene" which is a statement of intended use in gene therapy. The earlier office action mailed on 11/15/00 and 2/15/00 clearly states that The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (Anderson WF, Nature 392:25-30, 1998). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. For example, in original clinical trial to treat adenosine deaminase (ADA) deficiency, patients received a total of 11 infusions of genetically modified autologous T-lymphocytes along with polyethylene glycol (PEG)-ADA. After 7 years of therapy no definitive conclusion is drawn as to the contribution of gene therapy to the present state of health of patients (Anderson page 29 col.1, para.6). In instant case, considering the scope of therapeutic gene (as claimed), it is unclear whether the disease would be the result of the loss of gene product or is the result of altered gene product function. It

is even unclear whether the treatment of the disease associated with the gene (as claimed) would require increase or decrease in the expression of the gene product. Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claims 24-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is indefinite because it recites limitation "genome based on a first retrovirus" and "retrovirus on which the vector particle is based" in lines 2 and 5. It is unclear what does "genome based on a first retrovirus" and "retrovirus on which the vector particle is based" means in this context.

Claims 24 recites limitation "functional portion thereof". Similarly, Claims 26 and 27 recites limitation "a functional equivalent thereof". It is unclear what is a functional portion thereof and a functional equivalent thereof in this context.

Claim Rejections - 35 USC § 103

Claims 24-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lisziewicz (WO92/21750, 1992) in view of Hope et al (PNAS, 87:7787-7791, 1990) and Naldini et al (Science 272:263-267, 1996).

Liziewicz teaches a retroviral vector (MLV) incorporating HIV Rev/RRE system, wherein the RRE is located within the transcriptional unit of the foreign gene or within the transcriptional unit of the vector (page 6, line 21-32 page 9, line 1-4 and fig. 1-4). Liziewicz further teaches that the vector contain an internal promoters operably linked to the foreign gene and DNA sequence encoding the RRE (page 9, line 5-26). The cited art teaches that RRE can be inserted in the vector in the LTR, in front of the foreign gene, behind the foreign gene or within an intron of the foreign gene (page 9, line 5-11). The cited art teaches that the preferred LTRs include the MLV LTRs or HIV LTRs (page 8, line 5). The retroviral vector (MLV) as taught by Liziewicz include a strong promoter (HIV LTR) which is switched on in the presence of the virus or viral-transactivator protein (tat), but in the absence of viral infection does not express the encoded gene product (page 12, line 14-25 and fig-4, page 13, line 19-24). Therefore, Liziewicz clearly teaches a retroviral vector wherein the nucleotide sequence of interest is located within an intron in the transcription unit of a provirus and the gene expression is only limited to HIV infected cells.

However, Liziewicz does not teach splice donor (SD) and splice acceptor (SA) sites that flanks the provirus intron and gene of interest. In addition Liziewicz does not teach the use of internal promoter CMV to drive the expression of a gene of interest.

Hope et al teaches that HIV-1 transactivator Rev is a nuclear protein that regulates the expression of HIV transcripts by binding to the Rev response elements (RRE) present in the HIV transcripts. Hope et al further teaches a retroviral vector comprising splice donor sequence, RRE and splice acceptor sequences, wherein the gene of interest (CAT) is located within the splice donor and splice acceptor sites (page 7787, abstract; page 7788, fig-1). Furthermore, the

transcripts produced by this vector harbor a single intron, which contain CAT coding sequences (page 778, col.1. Para.1). The cited art further teaches the infection of MT4 cells with recombinant viral particles in vitro (page 21 col.2 para.2).

Naldini et al teaches a three plasmid retroviral expression system wherein the transfer vector comprising splice donor sequence, RRE and splice acceptor sequences (page 263, fig-1) In addition, Naldini teaches the use of internal promoter CMV to drive the expression of a gene of interest (page 263, fig-1). Naldini teaches that presence of RRE allows efficient transcription and cytoplasmic export of full length vector transcripts in the presence of HIV Tat and Rev regulatory proteins (page 263, col.2 para.1). Therefore, Naldini clearly teaches the use of splice donor sequence, RRE and splice acceptor sequences along with the use of a strong promoter (CMV) to drive the expression of gene of interest.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the retroviral vector (MLV) as taught by Liziewicz, by incorporating a nucleotides of interest within the splice acceptor site (HIV) as taught by Hope et al. One would have been motivated to do so because the insertion of a RRE (HIV) into the intron of foreign gene and within splice donor and splice acceptor sites provides the regulation of the expression of a foreign gene by RRE element which is only switched on in the presence REV protein. It would have been further obvious to modify the above vector by incorporating the CMV promoter as an internal promoter because CMV promoter is know to be strong promoter that would increase the expression of gene of interest. Therefore, the cited art clearly teaches the combination as claimed wherein the first retroviral vector (MLV) as taught by Liziewicz would have been modified in view of Hope and Naldini who teaches splice donor /splice acceptor, RRE/REV and LTR from a

second retroviral (HIV). One would have a reasonable expectation of success because the regulation of HIV LTR by Tat-protein and RRE by Rev-protein has been a well characterize phenomenon in the art at the time the instant invention was made. Therefore the invention as claimed is prima facie obvious in view of the prior art of record.

The applicant argues that there is no motivation to combine or modify the teaching of cited references. Naldini doe not disclose the benefits of controlling expression via the interactions of agents within a cell. The applicant further argues that Hope does not suggest Rev-inducible promoter activity. The applicant further argues that Liaziewicz makes no mention of modifying the promoter to eliminate low-level expression of the gene of interest (response, page 6). The applicant further argues that configuration of invention as claimed is very different from the configuration cited in the prior art vectors (response, page 8, ¶ 2). The applicant further argues that one skill in the art armed with the teaching of cited references would not have a reasonable expectation that creating claimed combination would function successfully to eliminate immune clearance problems associated with HIV gene (response, page 7, ¶ 3).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The applicant fails to consider the combined teaching of the reference cited herein in its entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. In instant case, Liziewicz clearly teaches a MLV retroviral vector incorporating HIV Rev/RRE system, wherein the RRE is located within the transcriptional unit of the foreign gene or within the transcriptional unit of the vector. Furthermore, the MLV retroviral vector as taught by Liziewicz include a strong promoter (HIV LTR) which is switched on in the presence of the virus or viral-transactivator protein (tat), but in the absence of viral infection does not express the encoded gene product. Furthermore, Hope et al teaches a retroviral vector comprising splice donor sequence, RRE and splice acceptor sequences, wherein the gene of interest (CAT) is located within the splice donor and splice acceptor. In addition, Naldini et al teaches a retroviral expression system wherein the transfer vector comprising splice donor sequence, RRE and splice acceptor sequences and CMV promoter internal promoter CMV that derive the expression of a gene of interest. Therefore the combination of cited art clearly teaches the use of splice donor sequence, RRE and splice acceptor sequences and LTR obtained from HIV (second retroviral vector of instant case), and the use of a CMV as an internal promoter to drive the expression of gene of interest in a MLV retroviral vector (first retroviral vector of instant case).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem.Yucel can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
Patent examiner

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER